Plasma Protein Therapeutics Association

April 23, 2012
Reference No.: FDAA12009

Division of Dockets Management (HFA-305) **VIA WEB**
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

SUBJECT: Draft Guidance for Industry on Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices [Docket No. FDA-2011-D-0868]

Dear Sir or Madam:

The Plasma Protein Therapeutics Association (PPTA) is pleased to provide these comments on the Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices: Draft Guidance ("Draft Guidance").[1] PPTA recognizes that these comments are being submitted after FDA's deadline of March 29, 2012, but hopes that, nonetheless, they will be considered by the Agency during its analysis of this important issue. PPTA understands that the Draft Guidance, in part, responds to the July 2011 citizen petition, filed on behalf of seven prescription drug manufacturers, seeking additional clarification on several areas of FDA policy regarding distribution of prescription drugs.[2] PPTA also understands that the Draft Guidance is the first of multiple draft guidances FDA plans to publish that address questions and issues related to emerging electronic media following the Agency's November 12-13, 2009, Part 15 public hearing on Promotion of FDA-Regulated Medical Products Using the Internet and Social Media Tools.[3]

About PPTA

PPTA is the international trade association and standards-setting organization for the world's major collectors of Source Plasma and manufacturers of plasma derived products and recombinant analogues, collectively referred to as plasma protein therapies, which are used in the treatment of a number of rare diseases. The diseases are often genetic, chronic, life-threatening conditions that require patients to receive regular infusions or injections of plasma protein therapies for the duration of their lives. The therapies include clotting-factor therapies for individuals with hemophilia A and B and other bleeding disorders; immunoglobulins to treat a complex of diseases in individuals with immune deficiencies; therapies for individuals who have alpha-1 anti-

[1] *See* Draft Guidance, Availability, 76 Fed. Reg. 82,303 (Dec. 30, 2011)
[2] *See id*. at 82,304
[3] *See id.*

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trypsin deficiency, which typically manifests as adult onset emphysema and limits substantially life expectancy; and albumin, which is used in emergency-room settings to treat individuals with shock, trauma, burns, and other conditions. PPTA members are committed to assuring the safety and availability of these medically needed, life-sustaining therapies.

General comments

PPTA commends FDA for holding the public hearing, publishing the Draft Guidance, and planning to publish additional draft guidances related to emerging electronic media. PPTA encourages FDA to publish and finalize this and the additional draft guidances as soon as possible as internet and other technologies are rapidly changing. PPTA also recognizes the need for additional clarification on at least some areas of FDA policy regarding distribution of prescription drugs as described in the citizen petition. In separate comments also submitted to FDA today, PPTA responds to the Agency's request for comments on "scientific exchange" also arising from the citizen petition. PPTA incorporates those comments here by reference. PPTA recognizes that FDA also has requested comments on the Agency's estimated annual reporting and recordkeeping burdens for responses to non-public and public unsolicited requests;[4] however, the Association does not have specific comments on these estimates at this time.[5] PPTA looks forward to additional opportunities to comment on future draft guidances related to emerging electronic media and on at least some of the remaining issues raised in the citizen petition.

PPTA supports access to all medically necessary plasma protein therapies

Off-label uses of prescription drugs including plasma protein therapies are lawful

In the Draft Guidance, FDA recognizes that, "once a drug … has been approved or cleared by FDA, generally, health care professionals can lawfully use or prescribe that product for uses or treatment indications that are not included in the product's approved labeling … ."[6] In fact, "[n]othing in [the Federal Food, Drug, and Cosmetic (FD&C) Act] shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship."[7] Similarly, 21 C.F.R. part 312 (FDA's regulations on investigational new drug applications) "does not apply to the use in the practice of medicine for an unlabeled indication of a new drug product approved under part 314 or of a licensed biological product."[8] Further,

[4] *See id*. at 82,304-06
[5] *See* this letter at 9 for general comments regarding burdens imposed by the Draft Guidance
[6] *See* Draft Guidance at 2
[7] 21 U.S.C. § 396
[8] *See* 21 C.F.R. § 312.2(d)

reimbursement is allowed by payors in federal health care programs for off-label uses that are "medically necessary";[9] in fact, when the use is a "medically accepted indication," reimbursement is mandated.[10] Such indications include those supported by one or more citations included or approved for inclusion in any of three compendia.[11]

Patients rely on medically necessary, off-label uses of plasma protein therapies

In the Draft Guidance, FDA also "recognizes that these off-label uses or treatment regimens may be important therapeutic options and may even constitute a medically recognized standard of care."[12] In fact, 21% of all prescription drug use[13] and, according to Journal of the American Medical Association physician-writer Tracy Hampton, 90% of prescription drug use for treatment of rare diseases is off-label. As noted, plasma protein therapies manufactured by PPTA members are used in the treatment of a number of rare diseases. Off-label uses of plasma protein therapies are not frivolous but are medically necessary uses as determined by patients' treating physicians. As such, these uses are vital to patient access.

FDA generally does not allow manufacturer statements promoting off-label uses

The FD&C Act prohibits firms[14] from introducing "new drugs" into interstate commerce for any intended use that FDA has not determined to be safe and effective[15] and ensures that the manufacturer's proposed labeling for a "new drug" is not "false or misleading in any particular."[16] The Act deems a drug misbranded "unless its labeling bears … adequate directions for use"[17] but exempts prescription drugs from the "adequate directions" requirement if the label contains "the directions for use and cautionary statements, if any, contained in such prescription."[18] The Act also authorizes FDA to promulgate regulations exempting certain drugs from the "adequate directions" requirement where the government finds the requirement "is not necessary for the protection of the public health."[19] As such, FDA has required for exemption that

[9] *See* 42 U.S.C. § 1396r-8(g)(1)(A)(ii)
[10] *See* 42 U.S.C. § 1396r-8(d)(1)(B)(i)
[11] 42 U.S.C. § 1396r-8(k)(6). The three compendia are the American Hospital Formulary Service Drug Information, the United States Pharmacopeia-Drug Information (or its successor publications), and the DRUGDEX Information System. 42 U.S.C. § 1396r-8(g)(1)(B)(i)
[12] *See* Draft Guidance at 2
[13] Liang *et al.*, Reforming Off-Label Promotion to Enhance Orphan Disease Treatment, *Science* 327 (5963): 273-74
[14] For the remainder of this letter, PPTA uses the terms "firm" and "manufacturer" interchangeably
[15] *See* 21 U.S.C. §§ 331(d), 355(a)
[16] *See* 21 U.S.C. § 335(d)
[17] *See* 21 U.S.C. § 352(f)(1)
[18] *See* 21 U.S.C. § 353(b)(2)
[19] *See* 21 U.S.C. § 352(f)(1)

"[l]abeling on or within the package from which the drug is to be dispensed bears adequate information for its use … for the purposes for which it is intended … ."[20] For FDA, "intended use" is informed by "the objective intent of the persons legally responsible for the labeling of drugs"; a manufacturer that "knows, or has knowledge of facts that would give him notice, that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it [must] provide adequate labeling for such a drug which accords with such other uses … ."[21]

In other words, if FDA determines that a manufacturer "objectively intends" off-label uses of its drug, then the drug is subject to the "adequate directions" requirement and, thus, is "misbranded" under the FD&C Act. FDA has based this determination

> not only on information provided "with" the product, but also … on information disseminated by manufacturers in other contexts, such as scientific and educational meetings and symposia, books, and articles, in part because all of these materials can create new intended uses for the products, which must be reflected in the labeling of the products.[22]

FDA believes that "[p]romotion of unapproved uses can encourage physicians and patients to make decisions based on statements or claims that are, in many cases, supported by little or no data."[23] As such, according to FDA, manufacturer statements that promote a drug for a use other than those approved or cleared by the Agency "may be used as evidence of a new intended use"[24] and, thus, of "misbranding."

FDA has recognized value of off-label information through multiple safe harbors

Off-label information is valuable

In the Draft Guidance, FDA recognizes that

> [s]cientific or medical departments within drug … firms often maintain a large body of information about their products [that] typically includes data and other information [that] may … include off-label information for their products. [S]uch information may … be of use to individuals seeking

[20] *See* 21 C.F.R. § 201.100(c)(1)
[21] *See* 21 C.F.R. § 201.128
[22] *See* Citizen Petition Regarding the Food and Drug Administration's Policy on Promotion of Unapproved Uses of Approved Drugs and Devices, Request for Comments, 59 Fed. Reg. 59,820, 59,821 (Nov. 18, 1994) ("1994 FR Notice")
[23] *See id.*
[24] *See* Draft Guidance at 2

> information about a medical product for themselves, patients, family members, or friends.[25]

FDA has confirmed the value of this information by establishing multiple safe harbors, *e.g.* responses to "unsolicited requests," "scientific exchange," distribution of reprints, continuing professional education.

FDA has established an "unsolicited requests" safe harbor

In the Draft Guidance, FDA recognizes that "firms are capable of responding to requests about their own named products in a truthful, nonmisleading, and accurate manner … and have robust and current information about their products … ."[26] PPTA agrees with FDA that

> it can be in the best interest of public health for a firm to respond to unsolicited requests for information about off-label uses of the firm's products that are addressed to a public forum, as other participants in the forum who offer responses may not provide or have access to the most accurate and up-to-date information about the firm's products.[27]

Since 1982, FDA has established and built on the "unsolicited requests" safe harbor through various policy documents, including Federal Register notices[28] and guidances.[29] FDA most recently noted the safe harbor in the Draft Reprint Guidance.[30]

FDA has established a "scientific exchange" safe harbor via regulation

21 C.F.R. § 312.7 prohibits sponsor or investigator representation "in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation" or other promotion of the drug.[31] However, "[t]his provision is not

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[25] *See* Draft Guidance at 2-3
[26] *See id.* at 3
[27] *See id.*
[28] *E.g.* 1994 FR Notice; Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64,074 (Dec. 3, 1997) ("Education Guidance FR Notice")
[29] *E.g.* Guidance for Industry-Supported Scientific and Educational Acivities [sic] (Nov. 1997) ("Education Guidance"); Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices: Draft Guidance (Feb. 2008) ("Draft Reprint Guidance"); Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices (Jan. 2009) ("Reprint Guidance")
[30] *See* Draft Reprint Guidance at 4, n. 3 (citing 1994 FR Notice)
[31] *See* 21 C.F.R. § 312.7

intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media."[32] FDA most recently delineated the "scientific exchange" safe harbor in the preamble to part of the final Investigational New Drug, Antibiotic, and Biologic Drug Product Regulations.[33]

FDA has established other safe harbors via guidances

The Draft Guidance notes that a firm can distribute reprints regarding off-label uses "without such dissemination being used as evidence of the firm's intent that the product be used for an unapproved use" under the final Reprint Guidance.[34] PPTA also notes that FDA has allowed discussions of unapproved uses as part of postgraduate and continuing professional education under the Education Guidance."[35]

"Unsolicited requests" safe harbor should be clear, predictable, and fair

PPTA members desire clarity, predictability, and fairness in FDA's application of its safe harbor. As described above, the Draft Guidance adds to a string of policy documents, each of which is subject to its own application and interpretation. PPTA asks that FDA take whatever steps are deemed necessary, including consolidation of numerous documents, to ensure the Agency's interpretation of its safe harbor is clear, predictable, and fair.

Recent First Amendment case law raises questions regarding FDA's off-label enforcement authority

PPTA notes the recent U.S. Supreme Court decision, *Sorrell v. IMS Health*,[36] which invalidated Vermont's Prescription Confidentiality Law restricting the sale, disclosure, and use of pharmacy records that reveal the prescribing practices of individual doctors. The law prevented "detailers" employed by pharmaceutical manufacturers from using prescriber-identifying information to market the manufacturers' brand-name drugs but permitted pharmacies to sell the information for purposes such as "health care research" and insurers, researchers, journalists, Vermont itself, and others also to use the information. The court found that the prohibited speech was protected by the free speech clause of the First Amendment and, because the law was designed to impose a specific, content- and speaker-based restriction, heightened judicial scrutiny was

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[32] *Id.*
[33] *See* Investigational New Drug, Antibiotic, and Biologic Drug Product Regulations, Treatment Use and Sale, 52 Fed. Reg. 19,466 (May 22, 1987) (providing requirements for and examples of "scientific exchange")
[34] *See* Draft Guidance at 3; Reprint Guidance
[35] *See* Education Guidance at 1-2
[36] 131 S.Ct. 2653 (2011)

warranted. Because Vermont's asserted interest in physician confidentiality could not justify the burden placed on the protected expression, the law was struck down.

FDA's current regulatory framework regarding manufacturer dissemination of off-label information restricts speech in a manner similar to the Vermont law. Thus, *Sorrell* questions the validity of the regulations under which FDA prohibits manufacturer dissemination of off-label information. In fact, Justice Steven Breyer, in *Sorrell*'s dissent, warns that "the same First Amendment standards that apply to Vermont here would apply to similar regulatory actions taken by … the Federal Government acting, for example, through [FDA] regulation."[37] Justice Breyer also gives FDA's off-label regulation as an example of a speaker-based restriction, similar to the Vermont law:

> Such a firm, for example, could not suggest to a potential purchaser (say, a doctor) that he or she might put a pharmaceutical drug to an "off label" use, even if the manufacturer, in good faith and considerable evidence, believes the drug will help. All the while, a third party (say, a researcher) is free to tell the doctor not to use the drug for that purpose.[38]

PPTA echoes these sentiments; the *Sorrell* opinion raises significant questions regarding the extent to which FDA may permissibly restrict manufacturer dissemination of off-label information.

Draft Guidance is too restrictive

As stated above, FDA most recently noted the "unsolicited requests" safe harbor in the Draft Reprint Guidance: "This draft guidance does not apply to scientific or medical information distributed in response to unsolicited requests for scientific or medical information from health care professionals."[39] In the final Reprint Guidance, FDA cites the Education Guidance FR Notice when noting that the Agency "has elsewhere stated its views on the dissemination of information regarding unapproved uses in responses to requests for scientific or medical information initiated solely by health care professionals."[40] The Education Guidance FR Notice provides FDA's most recent delineation of the safe harbor:

- Manufacturers "should provide limited technical support only in response to an unsolicited request for assistance from either the provider or a presenter."[41]

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[37] *See id.* at 2675-76
[38] *See id*. at 2678
[39] *See* Draft Reprint Guidance at 4, n. 3 (citing 1994 FR Notice)
[40] *See* Reprint Guidance at 3, n. 5
[41] Education Guidance FR Notice at 64,086

- "[I]nformation about the [manufacturer's] product presented in the scientific or educational activity [may be] further disseminated after the initial program or publication … in response to an unsolicited request … ."[42]
- "[M]aterials [may be] disseminated by the [manufacturer] in response to an unsolicited request … ."[43]

Because the U.S. Supreme Court has placed FDA's authority to restrict manufacturer dissemination of off-label information in question, FDA is compelled, at the least, to maintain its safe harbor policies, if not to expand them. While PPTA appreciates that FDA continues to recognize the existence of an "unsolicited requests" safe harbor in the Draft Guidance, post-*Sorrell* the document is too restrictive. FDA should indicate that the Agency will not use manufacturer statements about its drug that are in response to an "unsolicited request" as evidence of a new intended use, and, in light of *Sorrell*, should seriously consider expanding the safe harbor.

Further, the Draft Guidance is not comprehensive. PPTA recognizes that, particularly in light of emerging social media, FDA policy may not contemplate all potential scenarios. Thus, PPTA suggests that, as technologies change, guidance documents should be updated to provide examples of application of policy.

Specific sections

III. Determining Whether a Request is Unsolicited or Solicited

The Draft Guidance, FDA recognizes the value of allowing firms to respond to "unsolicited" requests for off-label information, although responses to "solicited" requests, *i.e.* those "prompted in any way by a manufacturer or its representatives," and the requests themselves are not allowed.[44] However, firms would lack guidance if a request appeared related to "scientific exchange," dissemination of reprints, and/or continuing professional education yet also "prompted in any way by a manufacturer or its representatives." Accordingly, PPTA suggests that a request and its response, if prompted by a manufacturer but in the context of another safe harbor, should be allowed.

Further, FDA's definition of "non-public unsolicited requests" is too restrictive.[45] Such requests should not be limited to "one-on-one communication[s]."[46] An unsolicited request may be directed privately to a manufacturer by a group of individuals, but such a request should not be considered public. As such, any distinction between a non-

[42] *Id.* at 64,091
[43] *Id.*
[44] *See* Draft Guidance at 4
[45] *See id.*
[46] *See id.*

public and public request should be based solely on whether it is in a private or public forum. Below, PPTA suggests that FDA develop cross-cutting standards for both non-public and public "unsolicited requests."[47] In that case, any non-public and public distinction would be most relevant in guidance documents providing examples.

V. Responding to Non-Public Unsolicited Requests for Off-Label Information Directed to Drug or Medical Device Firms

PPTA urges FDA to exercise caution in placing burdens on manufacturers in responding to non-public unsolicited requests, *i.e.* accompanying information and recordkeeping (recommendations 3, 6, and 7).[48] Before finalizing these provisions, FDA should consider *Sorrell* and the recognized value of off-label information, as well as any information in the docket from manufacturers regarding any practical implications of imposing such burdens.

VI. Responding to Public Unsolicited Requests for Off-Label Information, Including Those Encountered Through Emerging Electronic Media by Drug or Medical Device Firms

FDA has identified key considerations regarding emerging electronic media: "The Internet has revolutionized communication, information-sharing, information exchange among systems, and collaboration, enabling consumers to become more proactive about their health and safety [but] online content may not be accurate."[49] However, the Draft Guidance takes the wrong approach to addressing this problem. Instead of empowering the parties often best equipped to provide accurate information to the benefit of patients, the manufacturers themselves, the Draft Guidance hampers their ability to do so. Such an approach not only may negatively affect patients but also narrows the current "unsolicited requests" safe harbor, a direction discouraged by *Sorrell*.

In particular, the first two parameters under which manufacturers may respond to non-public unsolicited requests in the Draft Guidance are too restrictive and unduly burden the dissemination of valuable off-label information, particularly in light of *Sorrell*:

1. *If a firm chooses to respond to public unsolicited requests for off-label information, the firm should respond only when the request pertains specifically to its own named product (and is not solely about a competitor's product).*
2. *A firm's **public** response to public unsolicited requests for off-label information about its named product should be limited to providing the*

[47] *See* this letter at 10
[48] *See* Draft Guidance at 8-9
[49] *See id.* at 10

> *firm's contact information and should* ***not*** *include any off-label information.*[50]

FDA should not foreclose the opportunity for manufacturers to respond to public unsolicited requests for off-label information regarding classes of products or their own product that is unidentified or misidentified. Nor should FDA prohibit the dissemination of off-label information in a public forum, where the maximum number of patients can benefit.

To maximize clarity, predictability, and fairness, PPTA suggests that the parameters for responding to public unsolicited requests mirror those for responding to non-public requests. One possibility is combining and streamlining most of FDA's current public and non-public recommendations to provide one set of cross-cutting standards for responding to unsolicited requests for off-label information.[51] Distinctions between public and nonpublic fora could be addressed in guidance documents.

FDA should broaden the safe harbor to permit manufacturer corrections

Lastly, PPTA respectfully requests that FDA allow manufacturers to proactively correct inaccurate information regarding off-label use presented in public fora, a scenario not contemplated by the Draft Guidance. PPTA recognizes that, prior to the existence of the Internet, other public fora existed in which inaccurate information regarding off-label uses may have been presented. However, social media and other online tools have created new environments in which information can be corrected in real time and directed to relevant populations. Thus, PPTA encourages FDA to broaden its overall safe harbor policy, to take advantage of these technologies. Again, as technologies change, guidance documents should be used to provide examples of application of this safe harbor.

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[50] *See id.* at 11

[51] *E.g.,* information distributed in response to an unsolicited request for off-label information should be:

- Provided to the individual(s) making the request
- Tailored to answer only the specific questions asked
- Truthful, nonmisleading, and accurate
- Scientific in nature
- Generated by medical or scientific personnel independent from sales or marketing departments
- Provided by representatives who clearly disclose their involvement with a particular firm and
- Not promotional in nature

Conclusion

PPTA appreciates the opportunity to provide these comments on the Draft Guidance and looks forward to continued work with FDA on its efforts to address questions and issues related to emerging electronic media and to clarify some areas of FDA policy regarding distribution of prescription drugs. PPTA welcomes from FDA any questions regarding these comments and/or requests for additional information.

Thank you for your consideration.

Respectfully Submitted,

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